Docket No.: C2432.0069
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:

Ludger Grote et al.

Application No.: 10/598,114

Confirmation No.: 1212

Filed: July 3, 2007

Art Unit: 1617

For: METHOD OF TREATING AND DIAGNOSING SLEEP DISORDERED BREATHING AND MEANS FOR CARRYING OUT THE METHOD

Examiner: S. Javanmard

APPEAL BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

As required under § 41.37(a), this brief is filed within two months of the Notice of Appeal filed in this case on May 28, 2009, and is in furtherance of said Notice of Appeal.

This brief contains items under the following headings as required by 37 C.F.R. § 41.37 and M.P.E.P. § 1205.2:

I. Real Party In Interest
II Related Appeals and Interferences
III. Status of Claims

I. REAL PARTY IN INTEREST

The real party in interest for this appeal is:

the inventors, namely Ludger Grote, Jan Hedner and Kaj Stenlof.

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

A. Total Number of Claims in Application

There are 16 claims pending in application.

B. Current Status of Claims

1. Claims canceled: 14-21, 23, 25, and 27

2. Claims withdrawn from consideration but not canceled: None

3. Claims pending: 1-13, 22, 24, and 26

4. Claims allowed: None

5. Claims rejected: 1-13, 22, 24, and 26

C. Claims On Appeal

The claims on appeal are claims 1-13, 22, 24, and 26.

IV. STATUS OF AMENDMENTS

Applicant did not amend the claims after Final Rejection.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Sleep apnea is a condition characterized by the intermittent cessation of airflow at the nose and mouth during sleep. Central sleep apnea (CSA) is characterized by complete cessation of the activity of all respiratory muscles and obstructive sleep apnea (OSA), is where airflow is interrupted despite continuing respiratory neural drive.

The principal forms of treating or preventing OSA include surgery of the upper airway, intra-oral mandibular advancement devices and long-term treatment with positive airway pressure, a treatment involving application of a mechanical airway splint to

counteract airway collapse. Various forms of pharmacological agents , e.g. acetazolamide, tricyclic antidepressants, theophylline, progesterone, and topiramate, have also been employed.

The invention is based on the discovery that zonisamide, 1,2-benzisoxazole-3-methanesulfonamide, is effective in treating or preventing OSA. This compound was previously known as a anti-epileptic drug, and has also been considered as a potential anti-obesity agent and as an agent for treating neuropathic pain, and for having a potential effect in the treatment of Parkinson's disease.

The independent claims on appeal can be mapped to the specification, *inter alia,* as follows:

1. A method of treating or preventing Obstructive Sleep Apnea (OSA) (page 4, lines 9-11) including Central Sleep Apnea (CSA) (page 1, lines 23-24, and 29-30, and page 6, lines 3-5), comprising snoring, sleep apnea and other forms of sleep disordered breathing (page 4, line 10), that comprises the administration of a pharmacologically effective amount of zonisamide to a patient in need thereof (page 4, lines 11-12), with the proviso that said snoring, sleep apnea, and sleep disordered breathing caused by external mechanical obstruction of the airways, such as by mucus, is excluded (page 4, lines 12-15).

22. A protective patch comprising zonisamide in an amount therapeutically effective in the treatment of Obstructive Sleep Apnea (OSA) including Central Sleep Apnea (CSA), comprising snoring, sleep apnea and other forms of sleep disordered breathing, and a pharmaceutically acceptable carrier for transdermal or transmucosal administration, with the proviso that snoring, sleep apnea, and sleep disordered breathing

caused by external mechanical obstruction of the airways, such as by mucus, is excluded. (As an original claim, this is a part of the specification, and is further supported by page 1, lines 23-24, page 4, lines 9-15 and page 6, lines 3-5)

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The claims on appeal have been rejected under 35 U.S.C. § 103 over Hedner (WO 01/62243A1) in view of LaRoche (JAMA 2004).

VII. ARGUMENT

The condition known as sleep apnea is the intermittent cessation of airflow at the nose and mouth during sleep. Obstructive sleep apnea (OSA) is where airflow is interrupted despite continuing respiratory neural drive. Central sleep apnea (CSA) is the form where there is complete cessation of the activity of all respiratory muscles. The condition results in daytime sleepiness or various degree of cognitive dysfunction as well as various symptoms suggestive on non-restorative sleep. Cognitive and mood changes exert a substantial burden on general health of those with this condition. Moreover, cardiovascular complications, in particular hypertension, cardiac failure, myocardial infarction and stroke, are common in OSA. Further, OSA has been associated with increased insulin resistance, diabetes, obesity, changes in lipid metabolism and increased platelet aggregability. Such symptoms and complications are not confined to severe cases but also observed in cases of partial OSA and in OSA patients without apparent signs of daytime hypersomnolence.

The principal ways in which OSA has been treated or prevented include surgery of the upper airway, use of intra-oral mandibular advancement devices and long-term treatment with positive airway pressure (PAP), a treatment involving application of a mechanical airway splint to counteract airway collapse. Various pharmacological agents, e.g. acetazolamide, tricyclic antidepressants, theophylline, progesterone, and topiramate, have also been employed.

The inventors discovered that zonisamide, 1,2-benzisoxazole-3-methanesulfonamide, is effective in treating or preventing OSA. This compound was previously known as a anti-epileptic drug, and has also been considered as a potential anti-obesity agent, as an agent for treating neuropathic pain, and for having a potential effect in the treatment of Parkinson's disease. Prior to the claimed invention, it was not previously known to have any effect on OSA.

The claims on appeal related to the treatment of OSA with zonisamide and to a patch containing an effective OSA treating amount of zonisamide. They have been rejected as obvious over a Hedner PCT publication combined with an article by LaRoche.

The Hedner PCT publication relates to an invention by the current inventors and another which, like the instant application, relates to the treatment of sleep disorder breathing, including sleep apnea. However, the active agent disclosed in this reference is topiramate, 2,3:4,5-di-o-isopropylidene-β-D-fructopyranose sulfamate. There is no teaching or suggestion of zonisamide anywhere in this reference.

LaRoche is a literature review of anti-epileptic drugs. Both zonisamide and topiramate are such agents. There is no teaching or suggestion relating to OAS anywhere in this reference.

Despite the facts that the first reference which teaches using of topiramate to treat sleep apnea has no teaching relating to zonisamide, and the second reference which has disclosure relating to topiramate and zonisamide has no disclosure relating to sleep apnea, it is asserted that in combination, they render the claimed invention obvious. The rationale of the rejection is that topiramate and zonisamide are both antiepileptic agents having a common mechanism of action and therefore a skilled person would be motivated to substitute one for the other when treating sleep apnea with a reasonable expectation of success.

For an obviousness rejection to be valid, there must be an apparent reason to undertake the combination, and that reason must be stated so that its validity can be examined. *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007). It is also important to "be aware, of course, of the distortion caused by hindsight bias...." *Id.* at 1397. The Examiner has properly stated the reason being advanced, namely that the fact that topiramate and zonisamide are both antiepileptic agents having a common mechanism of action would motivate the skilled person to substitute one for the other when treating sleep apnea with a reasonable expectation of success. However, the proposed reason for substitution is not valid, and there is no "predictable solution" having a reasonable expectation of success.

A basic deficiency in the rationale advanced is that it improperly crosses the line where simplification of a reference for description purposes becomes a modification of the

reference's disclosure. *Medtronic, Inc. v. Cardiac Pacemakers, Ind.*, 220 USPQ 97, 103 (Fed. Cir. 1983). The modification here lies in the assertion that Laroche shows the two compounds have identical mechanisms of action.

A skilled person may have a reasonable expectation of success for predicting that a substitution of one compound for the other would be effective when two compounds have identical mechanisms of action, absent other factors. But that is not the present factual situation because the two compounds do not have identical mechanisms of action. LaRoche shows in the figure on page 607 that that topiramate exhibits potentiation of GABA activity and antagonism of glutamate, but zonisamide does not exhibit the same activity. Thus, the mechanisms of action are not exactly the same. That means the rationale for the rejection, i.e., both have the same mechanisms of action, is not correct.

A rationale based on common activity for treating a different condition coupled with only some degree of common mechanism of action is a justification based on impermissible hindsight and speculative reasoning unless the mechanisms which both zonisamide and topiramate exhibit are relevant to the treatment of the conditions claimed, which is OSA here. Such a rationale, of necessity, requires that the mechanism of action by which OSA is treated or prevented is known. It is axiomatic that if relevant mechanism of action is not known, there is no factual basis for substituting one compound for the other nor can there be any reasonable expectation of success to do so. The record in this appeal establishes that the mechanism by which sleep apnea can be treated unknown.

The Hedner reference states at page 2, line 14 that the "patophysiology of OSA is virtually unknown." That statement alone establishes that how an OSA treating agent

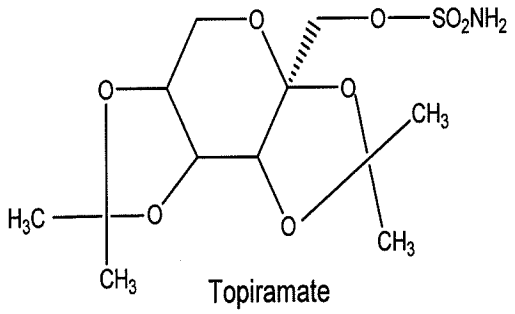
works is not known. Later, in a paragraph beginning at page 4, line 28, and using language which clearly indicates that what is being said is nothing more than speculation, it is said that the effect of topiramate "may be due to one or more" of its pharmacological actions, or that "a single action or several of these actions in concert may" increase respiratory neurones drive or their firing. While the use of the words "may be" is sufficient to make it clear that only conjecture is being advanced, the same paragraph further warns at page 5, lines 3-5 that "it must be emphasized that ["scientifically attractive explanations for the observed effect of topiramate" in treating OSA] must not be considered binding in any way on the concept or the working of the present invention".

The indication in the Hedner reference that the mechanism was not know is reinforced and confirmed by the Declaration of record by three of the Hedner reference inventors in which they say they were not aware of any knowledge in the art which even suggested that the mechanisms both compound exhibited, blocking sodium and T-type calcium channels, was involved in the treatment of OSA.

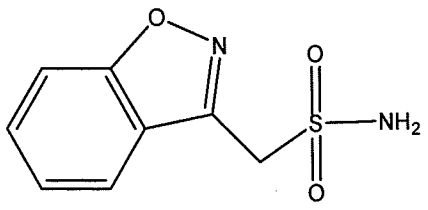
The only reference having anything to do with mechanism is LaRoche and that disclosure concerns epilepsy, not sleep apnea. Even as to the epilepsy utility, the relevant mechanism of action is not known since LaRoche teaches the known active epileptic agents have a highly variable and different mechanism of action. The figure on page 607 of LaRoche shows that topiramate effects sodium channels, calcium channels, GABA potentiation and glutamate antagonism. Zonisamide, on the other hand, exhibited effects on sodium and calcium channels only. LaRoche teaches that looking at the mechanism of action of antiepileptic compounds would not have been predictive even though epileptic

activity testing showed the compounds were active. Even looking at this reference through rose coloured glasses, one finds a disclosure that topiramate and zonisamide have a different mechanisms of action even as to treating epilepsy.

Zonisamide, topiramate, and other antiepileptic drugs lack a common structural element, as illustrated in the Formula Sheet in Appendix B and below.



Topiramate



Zonisamide

That means their pharmaceutical effect, antiepileptic or otherwise, also cannot be predicted with a reasonable expectation of success from their structure.

Where there is at least some knowledge about the mechanism by which an active agent is effective to treat a particular condition, as there is with epilepsy, it may be argued that it would be obvious to try an agent which has mechanism in common with some expectation of success. Conversely, when there is no knowledge about the mechanism by which an active agent is effective to treat the condition, as the record here establishes with OSA, the skilled person could not have any expectation of success, much less the required reasonable expectation of success.

Neither the references themselves nor any other information in the record of this case indicates that a person skilled in this art knew or even believed such sodium or calcium blocking was the relevant mechanism of action in treating OSA. This is a critical deficiency in the rejection under review because it means that the factual basis for any expectation of success based on blocking is silence, and that is not a valid basis. *In re Newell*, 13 USPQ2d 1248, 1250 (Fed. Cir. 1989)("Obviousness cannot be predicted on what is unknown."); *In re Burt*, 148 USPQ 548, 553 (CCPA 1966). Topiramate may useful to treat OSA, but there is nothing which indicates to a person skilled in the art, how or why that result is achieved. Coupled with the fact that zonisamide does not have the identical mechanism of action as topiramate, there is nothing which would motivate the skilled person to try a substitution or to have a reasonably expectation of success, much less both.

Even if the mechanism proposal on which the rejection is based was not merely rank speculation and had some basis, and it does not, the record here also establishes that the proposal is wrong. The proposal underlying the rejection is that because both zonisamide and topiramate exhibit one type of activity (anti-convulsant) and have blocking sodium and T-type calcium channels activity in common means all people needing a different type of activity (treating OSA) will react in the same way to both drugs. However, the Declaration of the applicants (Appendix B) shows that the hypothesized expectation of some degree of success in all instances is wrong. Three of the 4 patients responded to one drug but not the other. Two patients responded to zonisamide but not to topiramate while the opposite was found in one patient. The fourth patient responded to both therapies. This is shown in the following table:

Patient number	1	2	3	4
Zonisamide	+	+	+	-
Topiramate	-	-	+	+

The Advisory Action criticizes the size of patient pool, but even though it is small, the results clearly show that individual effects of these two compounds are unique and that an effect with one of the compounds does not imply or suggest that the other agent is effective.

Moreover, the dose of zonisamide was double that of topiramate. If the theory on which the rejection is based is correct, i.e., both are acting by the same mechanism, there would be a response to zonisamide in every single instance and without exception when there was a response to the lesser amount of topiramate. But a response did not always occur. These results show that the rationale on which the rejection is based is wrong. The data also establishes that a commonality of antiepileptic activity, regardless of the reason for that commonality, does not permit a prediction with a reasonable expectation of success that zonisamide will be active for treating OSA because topiramate is so active.

All of the foregoing considerations establish that zonisamide represents a novel, unobvious and unique therapeutic modality in sleep apnea. The activity of the compound to treat or prevent sleep apnea is not predictable, nor is a patch containing a therapeutically effective amount of the drug for use in treating or preventing sleep apnea predicable. The claimed invention is unobvious.

The Final rejection should be reversed.

VIII. CLAIMS

A copy of the claims involved in the present appeal is attached hereto as Appendix A.

Dated: July 28, 2009

Respectfully submitted,

By Edward A. Meilman

Edward A. Meilman
Registration No.: 24,735
DICKSTEIN SHAPIRO LLP
1633 Broadway[1]
New York, New York 10019
(212) 277-6500
Attorney for Applicant

[1] Please note this is a new mailing address

APPENDIX A

Claims Involved in the Appeal of Application Serial No. 10/598,114

1. A method of treating or preventing Obstructive Sleep Apnea (OSA) including Central Sleep Apnea (CSA), comprising snoring, sleep apnea and other forms of sleep disordered breathing, that comprises the administration of a pharmacologically effective amount of zonisamide to a patient in need thereof, with the proviso that said snoring, sleep apnea, and sleep disordered breathing caused by external mechanical obstruction of the airways, such as by mucus, is excluded.

2. The method of claim 1, wherein said therapeutically effective dose is effective during a substantial portion of a single sleep period.

3. The method of claim 2, wherein said substantial portion is 50% or more of said sleep period.

4. The method of claim 2, wherein said substantial portion is 80% or more of said sleep period.

5. The method of claim 2, wherein said single sleep period is from one hour to ten hours.

6. The method of claim 1, wherein the administration is peroral.

7. The method of claim 6, wherein the administration is sublingual.

8. The method of claim 1, wherein the administration is topical.

9. The method of claim 6, wherein the administration is confined to the frontal portion of the neck and the breast.

10. The method of claim 6, wherein the therapeutically active dose is released from a composition for controlled release over a period of time extending from 1 hour to 12 hours and more.

11. The method of claim 1, wherein from 50% to 100% of said therapeutically effective dose is released within a period of three hours from administration.

12. The method of claim 1, wherein from 80% to 100% of said therapeutically effective dose is released within a period of five hours from administration.

13. The method of claim 10, wherein said therapeutically effective dose is from 50 to 800 mg.

22. A protective patch comprising zonisamide in an amount therapeutically effective in the treatment of Obstructive Sleep Apnea (OSA) including Central Sleep Apnea (CSA), comprising snoring, sleep apnea and other forms of sleep disordered

breathing, and a pharmaceutically acceptable carrier for transdermal or transmucosal administration, with the proviso that snoring, sleep apnea, and sleep disordered breathing caused by external mechanical obstruction of the airways, such as by mucus, is excluded.

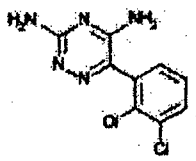
24. The method of claim 1, comprising the administration of one or more additional compounds effective in the treatment of OSA or CSA. [[.]]

26. The patch of claim 22, comprising one or more additional compounds effective in the treatment of OSA or CSA.

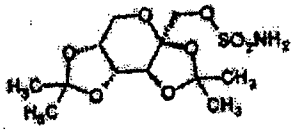
APPENDIX B

The evidence pursuant to §§ 1.130, 1.131, or 1.132 or entered by or relied upon by the examiner is a Declaration by the inventors, and a sheet showing the structure of the compounds of the LaRoche reference.

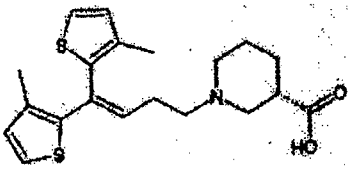
Formula Sheet - "New Antiepileptic Drugs" , S M LaRoche et al., JAMA, 2004



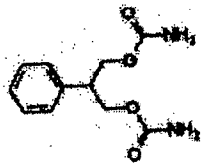
lamotrigine



topiramate



tiagabine



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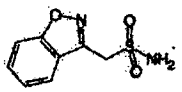
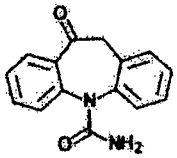


zonisamide



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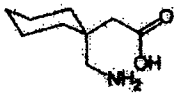
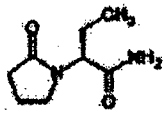


gabapentin



levetiracetam